Bandolier 40

What do we think?
What do we know?
What can we prove?

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BANDOLIER 2ND ANNUAL

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HOPE SPRINGS

A dusty ***Bandolier*** has returned from a surfeit of recent scientific and clinical meetings. There were some good talks and some not so good talks. Sometimes there seems to be a gulf between the scientific inquiry and the everyday needs of people. Patients hope to get better, and researchers hope their work will help (and hope it will help to further their careers, too). Too often hope is the only link between the patient and the researcher.

There are glorious exceptions, the times when research and clinical need come together to create hope when previously there was none. The best current examples are the exciting developments taking place in HIV infection and AIDS, where new treatments and tests combine to hold out hope for improvement and perhaps more. ***Bandolier*** is following these developments with interest, and hopes (that word again) to write about them shortly. Perhaps when these triumphs first emerged ***Bandolier*** would have failed to predict their triumphant future.

Many people, and their relatives and carers, have to cope with awful symptoms and disabilities. Hope is important for them, and a nursing review of hope (page 7), while it provides no numbers-needed-to-treat, or indeed any numbers, at least provides a starting point for those interested in this special aspect of the relationship with our patients.

Patients and others find hope in the trumpeting of research findings in the media, and the uncritical appraisal of launches of new interventions. An example is that of donepezil (Aricept) in Alzheimer's disease. As ***Bandolier*** reported last month (#39), professionals are placed in a real bind having to advise patients with less than adequate information. We frogs need clear help with all this stuff which keeps landing in our jam jar. ***Bandolier*** this month (page 2) reaches up from the slime at the bottom of the jar and bites the bullet (acknowledging the mixed metaphor).

Squaring the circle

How should health services manage innovation? There are real problems with both the ***range*** of information - the innovation may be a drug, an operation, a new diagnostic test, or a management change - and the ***quantity -*** one new drug is licensed about every 10 days. Some new knowledge will itself challenge the ***way*** in which we do things, not just ***what*** we do. Perhaps this is the section of the circle which we need to square. We tend to focus on the scientific advance - sometimes not asking which scientific advance would be most helpful - and then blink in astonishment when the advance arrives and we can't afford it. Nothing new here, and these things - the very necessary advance and the slightly less necessary advance, shouldn't be exclusive - trouble is they are when we haven't got unlimited money.

Philosophical in the bath

Bandolier has a Celtic distrust of philosophers, believing that some activities are best restricted to bath time, but offers some wise words attributed to Bertand Russell, via David Grahame-Smith.

- Never feel absolutely certain of anything.
- Never discourage thinking, for one will always succeed.
- Have little respect for the authority of others, for there are always contrary authorities to be found.
- Do not fear to be eccentric of opinion for every opinion was once eccentric.
- Find pleasure in intelligent dissent, rather than passive agreement, for the former implies a deeper agreement than the latter.
- Do not feel envious of the happiness and contentment of those who live in a fool's paradise for only a fool will think it is paradise.

In this issue

NEW DEMENTIA DRUG

Donepezil (Aricept) is an expensive new drug for the treatment of dementia, costing about £1,000 per patient per year. Its recent introduction has raised questions not only about whether the drug is effective and cost-effective, but also about the extent of evidence that should be available before a new agent is licensed by the regulatory authorities.

Background

Dementia is perhaps the psychiatric disorder of greatest public health importance, with an approximate UK prevalence of 5% at age 65, rising to 20% in the over 80s. It is a progressive, global loss of mental function (concentration, memory and orientation) occurring in clear consciousness. Most cases are due to the degenerative process of Alzheimer's disease (loss of brain cells generally, especially those containing acetylcholine) or to cerebrovascular disease (multi-infarct dementia).

Drug treatment

Various types of drug including antidepressants and antipsychotics are used for symptomatic treatment of dementia. As for specific treatment, reversing the degeneration of nerve cells continues to seem a tall order, and drug research has concentrated on boosting the presumed failure of acetylcholine function in the brains of Alzheimer sufferers, by blocking the enzyme which breaks down acetylcholine. The problem here is that cells containing acetylcholine are found throughout the body, not just in the brain, so side effects are likely.

Donepezil

There is currently only one published trial of this acetylcholine esterase inhibitor, a "preliminary dose-ranging study" [1] from the clinical science department of the manufacturer. It compared donepezil at three doses (1, 3 and 5 mg) with placebo. It was randomised and double-blind for 12 weeks, followed by a two-week single-blind open-label washout. The main analyses were at the "endpoint", which is not defined clearly. There were 40 patients per group, but as it is sold as 5 mg and 10 mg tablets, the main comparison involved only 80 patients.

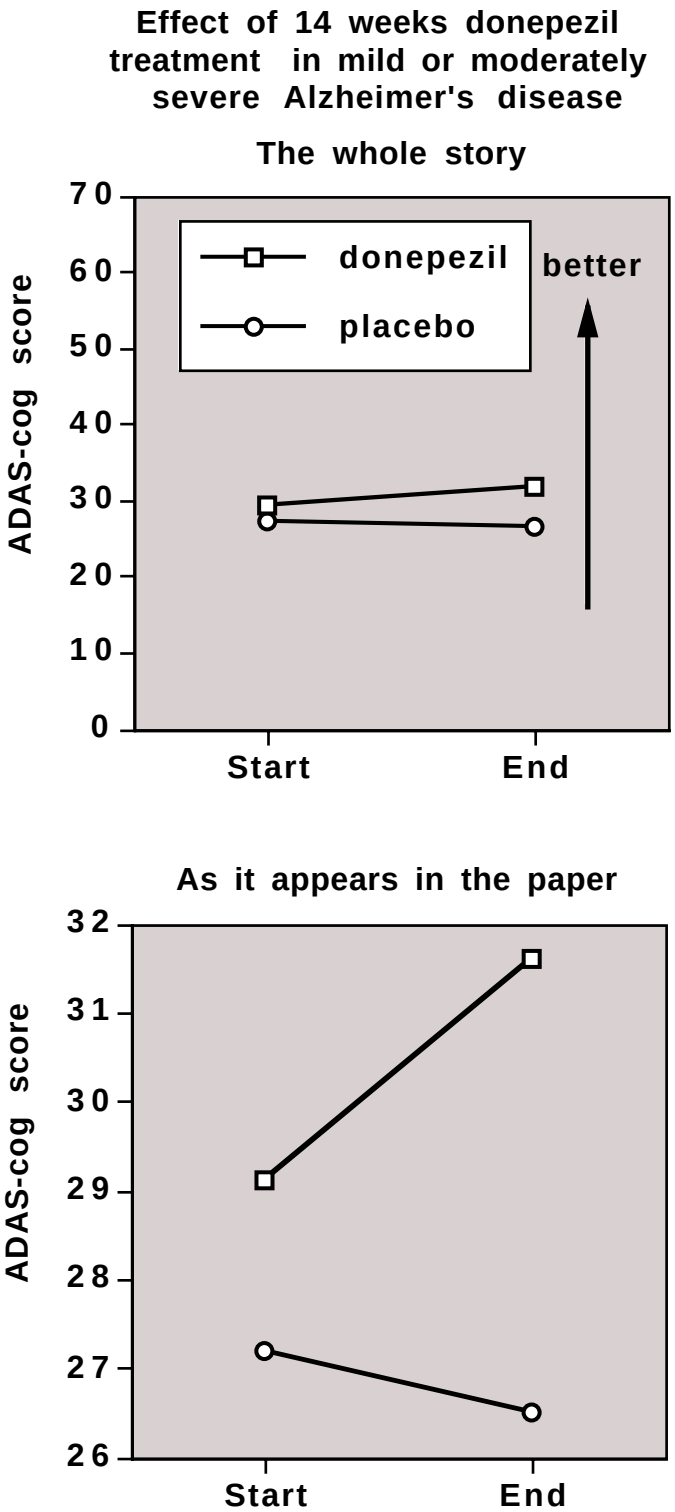
Outcome

The primary outcome measure was the group mean score on the 70-point ADAS-cog, an observer-rated scale measuring cognitive function, in which higher scores are better. Other scales were used, including quality of life indicators.

Results

You will search long and hard to find a definition of a clinically useful outcome, the number of patients who benefited, and whether that benefit was sustained in those patients. So no NNTs for donepezil. What we do have is lots of statistics in a vacuum.

There was a small average decline in the ADAS-cog score in those receiving placebo (of 0.7 on a 70-point scale, with a range of change from a fall of 7 points to an increase of 14.5 points), and a small average increase in those on 5 mg donepezil (2.5 on a 70-point scale, with a range of change from a fall of 8 points to an increase in 7 points). The difference was statistically significant. The way in which these results are presented can over-emphasise the differences, as the two graphs show. The top graph shows the whole story, with the 70-point ADAS-cog scale. The bottom graph is roughly how the results were presented in the paper [1].



There were a number of secondary outcomes, some of which showed changes. There was no effect of the drug on the quality of life as assessed by the carers.

A cold and fishy eye

Anyone looking at this study with a cold and fishy eye would be understandably sceptical. Extrapolating a useful clinical response to a new drug from a single small trial of limited duration and demonstrating limited efficacy is impossible. We should ask whether this really amounts to evidence of sufficient strength on which to change practice. There are, though, two unpublished randomised, double blind, placebo controlled studies of 5 mg and 10 mg donepezil, each with about 150 patients per group. According to the UK Drug Information Service [2], both doses of donepezil show overall changes of smaller magnitude than the published study.

Donepezil trials

Trial	Number	5 mg donepezil Δ ADAS-cog	10 mg donepezil Δ ADAS-cog
[1]	161 - 12 weeks	3.2	not given
A302	450 - 24 weeks	2.8	3.1
A301	450 - 12 weeks	2.7	3.0

All randomised, double-blind studies in patients with mild to moderately severe Alzheimer's disease. Δ ADAS-cog scores are the difference between treated and placebo patients at the end of the study.

It might be argued that because when donepezil is stopped, the small difference in scores disappears, it could maintain improvements over longer periods. But there is little evidence for this.

The appropriate question is different. Are there any patients who do very well with this drug? Again, there is no convincing evidence. There is little consensus on what change on an ADAS-cog score indicates clinical significance. The lowest value seems to be 4 points. Even on that basis the majority of patients will not have any clinical benefit (as the quality of life results judged by the carers indicates). If clinical benefit was associated with a larger change on the scale than 4 points, then only a small minority would benefit.

Licensing new drugs: have we got it right?

Prescribers are in an unenviable position. On the one hand, they will face pressure from patients, relatives and heavy promotion to try a new treatment in a condition of otherwise grim prognosis. On the other hand, the evidence that the drug is effective appears scanty. There is an additional ethical dimension in that many patients will not be able to give truly informed consent about whether they wish to accept these uncertainties.

The UK licensing procedure requires a new drug be manufactured to an acceptable quality, have an acceptable safety record, and be efficacious. Should it be extended, so that an independent agency assesses on behalf of the NHS, whether it is sufficiently well-researched and has acceptable cost-utility for it to be routinely available in the NHS?

Bandolier cannot, of course, answer this question, but the debate will continue, in these pages and elsewhere, notably on the evidence-based-health mailing list [3], where many of these ideas have been aired.

A comment and a suggestion

The conclusion is that donepezil probably produces an improvement corresponding to "turning the clock back" by about three or six months. The benefits are small, and the weight of evidence is unconvincing.

Perhaps this is an opportunity for industry and health service to come together to ask some sensible questions about how we do things. ***Bandolier*** suggests setting some prior standard, agreed by consensus , of what constitutes an acceptable and worthwhile change on the ADAS-cog score. Then manufacturers should be challenged to make the individual patient data from the three randomised trials available for single-patient meta-analysis against that consensus. We might then have a clearer picture of what the "true" effect is, and even see if it is possible better to predict patients in whom this benefit will be found. The alternative will be a slanging match with patients and carers in the middle.

References

1 SL Rogers, LT Friedhoff. The efficacy and safety of donepezil in patients with Alzheimer's Disease. Dementia 1996 7: 293-303.
2 Donepezil. UK Drug Information Services. Monograph 4/97/12
3 http://www.mailbase.ac.uk

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ANGINA

"There is a disorder of the breast marked with a strong and peculiar symptoms considerable for the degree of danger belonging to it and not extremely rare of which I do not recollect any mention among medical authors. The seat of it and sense of strangling and anxiety with which is attended may make it not improperly be called Angina pectoris. Those who are afflicted with it, are seized, while they are walking, and more particularly when they walk soon after eating with a painful and most disagreeable sensation in the breast."

So William Heberden, is some nice 18th century language, first described angina in 1768.

Drawing the line

Bandolier readers who ask about angina don't have problems diagnosing it, but they do ask about how best to treat it. Now there we have to draw the line. It simply is not possible to do that for a multitude of obvious reasons. What ***Bandolier*** can do is to look for evidence, signpost it, and précis it. This might not give all the answers: indeed, it never can. But it can help to inform.

For angina we found one large trial which compared a ß-blocker (bisoprolol) with a calcium antagonist (nifedipine).

TIBBS

This refers to the Total Ischaemic Burden Bisoprolol Study [1], which was a multicentre trial comparing bisoprolol and nifedipine. It was randomised and double-blind (but perhaps not completely so). Patients were predominantly men with an average age of just under 60 years.

Six hundred and thirty one patients with stable angina and exercise stress tests showing electrocardiogram changes went into a placebo pre-phase. They underwent 48 hour ambulatory electrocardiogram monitoring. The 330 patients with two or more transient ischaemic episodes in 48 hours were randomised to either bisoprolol (4 weeks at 10 mg once daily, followed by 4 weeks of 20 mg once daily) or slow release nifedipine (4 weeks at 20 mg twice daily followed by 4 weeks at 40 mg twice daily). That is, for both treatments there was a low dose phase and a high dose phase.

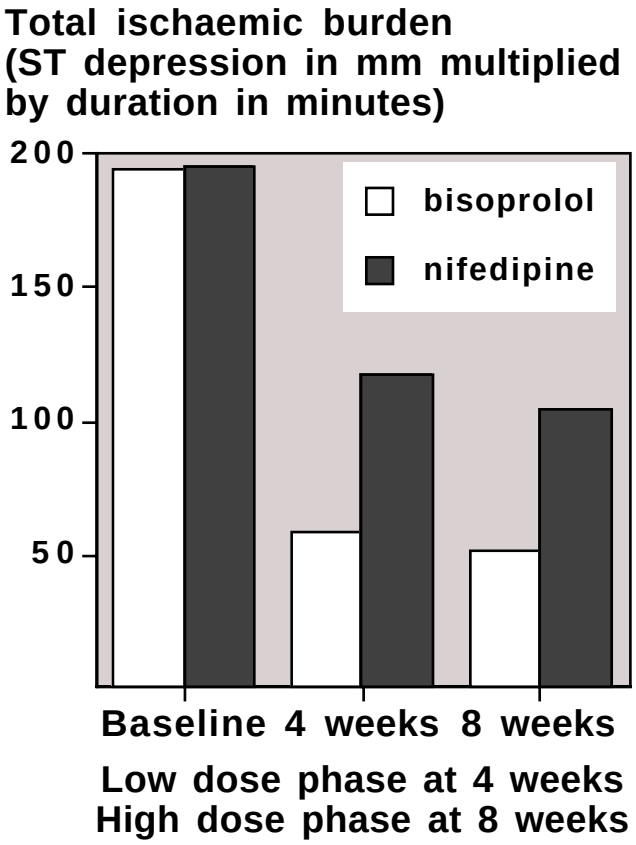
Two consecutive 24 hour ambulatory electrocardiogram recordings were taken at the end of four weeks (low dose phase) and at the end of eight weeks (high dose phase). All recordings were read blindly in a single laboratory, and only those tapes with at least 75% of the recorded data were used.

Outcomes

There were a number of different outcomes, the main one being total ischaemic burden (ST segment depression in millimetres multiplied by the episode duration in minutes). The number of patients who had episodes of transient ischaemia reduced by 25%, 50%, 75% and 100% was also reported.

Results

The total ischaemic burden dropped (from the same initial level during the placebo phase) by 73% after eight weeks on bisoprolol and by 46% after eight weeks on nifedipine, indicating that ischaemia, measured by ST segment depression and duration, was reduced. The means are shown below.



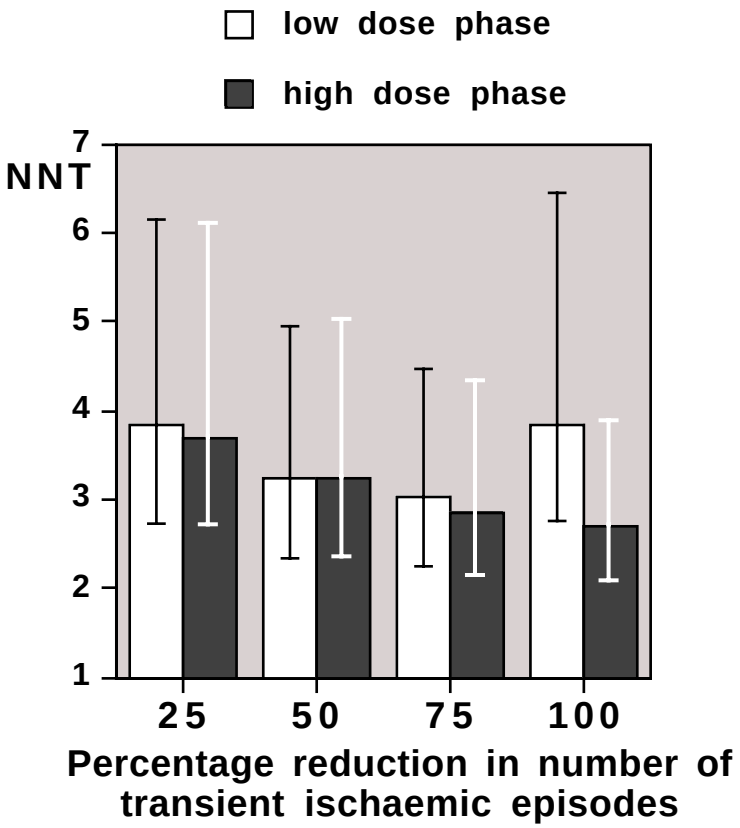
By using the numbers of patients who had reductions of 25%, 50%, 75% or 100% in the number of transient ischaemic attacks it is possible to calculate NNTs at each level and following low dose phase (4 weeks) and high dose phase (8 weeks) regimens.

Thus at eight weeks the NNT was 2.7 (2.1 to 3.9) for complete cessation of asymptomatic transient ischaemic episodes with 20 mg daily bisoprolol compared with 40 mg twice daily slow release nifedipine in patients with stable angina. This means that one of every three patients with stable angina will have complete cessation of ischaemic attacks with bisoprolol who would not have done so if they were taking nifedipine.

Response and prognosis

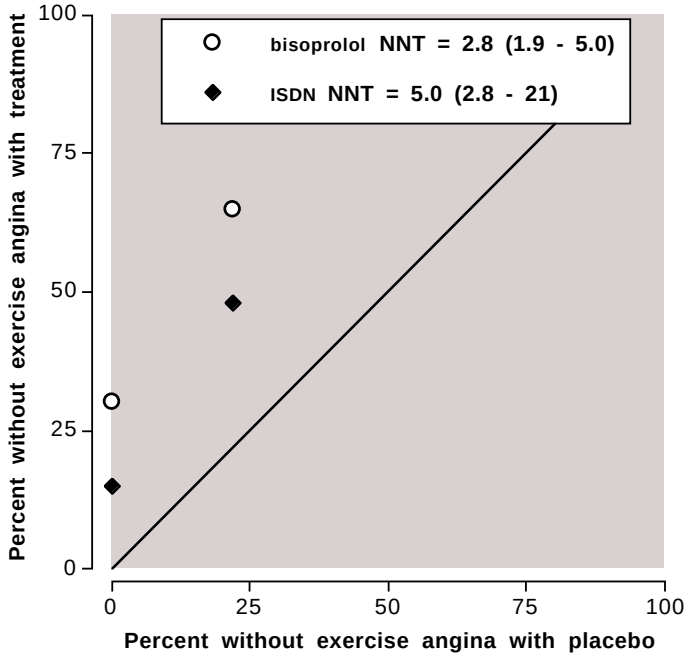
A follow up to the TIBBS study [2] looked at consequences one year after the end of the study. The follow-up was of 520 of 545 patients screened, which included the 330 who took part in the study. Information was collected on 'hard' events (cardiac and non-cardiac death, nonfatal acute myocardial infarction, hospital admission for unstable angina) and 'less hard' events (need for bypass surgery or coronary angioplasty, which are subject to a degree of bias).

Number of patients with stable angina pectoris who have to be treated with bisoprolol compared with nifedipine to produce different levels of reduction in transient ischaemic episodes in one of them



The L'Abbé plot shows that bisoprolol produced fewer patients with angina attacks. Pooling the results from the two trials, the NNT was 5.0 (2.8 - 21) for 20 mg ISDN three times a day compared with placebo to produce one patient free of exercise induced angina after four to six weeks of treatment. For bisoprolol 10 mg once a day it was 2.8 (1.9 - 5.0).

Angina-free patients on exercise testing: bisoprolol and isosorbide dinitrate (ISDN) compared with placebo



The results are interesting because they give a picture of the natural history of angina. The main findings were:-

1. In patients with more than six ischaemic episodes at baseline, an event occurred in 33%, compared with 25% in those with two to six episodes, and 13% with those with fewer than two episodes.
2. Hard events were more frequent (12%) in patients with two or more ischaemic episodes, compared with only 5% in those with fewer than two episodes.
3. Patients with a 100% response rate of transient ischaemic episodes during the TIBBS trial had a 18% event rate at 1 year compared with 32% for non-100% responders.
4. Patients randomised to bisoprolol had a lower event rate at one year (22%) than those randomised to nifedipine (33%), which may have reflected the influence of reduced ischaemic burden during the trial, or the more frequent use of ß-blockers after the trial stopped in those initially randomised to bisoprolol (47%) than those randomised to nifedipine (32%).

Comparison with nitrates

Two studies [3,4], both from the same group in Groningen, compared placebo with isosorbide dinitrate (ISDN) and bisoprolol in randomised, double bind, crossover comparisons. Once daily 10 mg bisoprolol was compared with 20 mg ISDN three times a day for four or six weeks. A common outcome was the number of angina-free patients during exercise testing at the end of a treatment period.

References:

1 T von Arnim. Medical treatment to reduce total ischaemic burden: total ischaemic burden bisoprolol study (TIBBS), a multicentre trial comparing bisoprolol and nifedipine. Journal of the American College of Cardiologists 1995 25: 231-8.

2 T von Arnim. Prognostic significance of transient ischaemic episodes: response to treatment shows improved prognosis. Journal of the American College of Cardiologists 1996 28: 20-4.

3 MCM Portegies, J Brouwer, L van de Ven, et al. Effects of bisoprolol and isosorbide dinitrate on the circadian distribution of myocardial ischaemia. Current Therapeutic Research 1995 56: 1225-36.

4 L van de Ven, A Vermuulen, J Tans et al. Which drug to choose for stable angina pectoris: a comparative study between bisoprolol and nitrates. International Journal of Cardiology 1995 47: 217-23.

Promoting patient choice

This two-day conference to be held under the auspices of the King's Fund in London on October 30/31 1997 is open to everyone. It aims to encourage public debate and stimulate developments in the areas of shared clinical decision-making and patient choice.

Further details from Pat Tawn, King's Fund, 11-13 Cavendish Square, London W1M 0AN. Tel 0171 307 2672.

THYROID INCIDENTALOMAS

Bandolier has previously carried information about incidentalomas, disorders found by sophisticated and highly sensitive imaging techniques which were hitherto undiscovered and whose significance is unknown (***Bandolier*** 10).

Thyroid imaging

A new paper from the Mayo Clinic [1] has shown another fascinating example of the problems caused by highly sensitive imaging. This was a review of all relevant articles on the identification of thyroid nodules. The authors called non-palpable nodules "incidentalomas" and found that most nodules that are bigger than 1 cm diameter can be palpated, particularly if they are on the surface of the thyroid gland.

Two autopsy studies with a combined total of 1033 individuals with clinically normal thyroids found a prevalence of 46% of them with at least one nodule.

Modern ultrasonography has the sensitivity to detect lesions as small as 1 to 3 mm. So it is possible to identify non-palpable nodules in anything between 13% and 50% of people in whom nodules cannot be identified by palpation.

Prospective studies of randomly selected patients have shown that up to 67% of people can be shown to have nodules when the thyroid gland is incidentally scanned, for example during carotid ultrasonography. It nicely brackets the 46% autopsy figure.

When is a nodule solitary?

In patients in whom solitary nodules were detected clinically, between 20 and 48% of patients were shown to have additional nodules on ultrasonography (34% overall in 456 patients).

So what does it all mean?

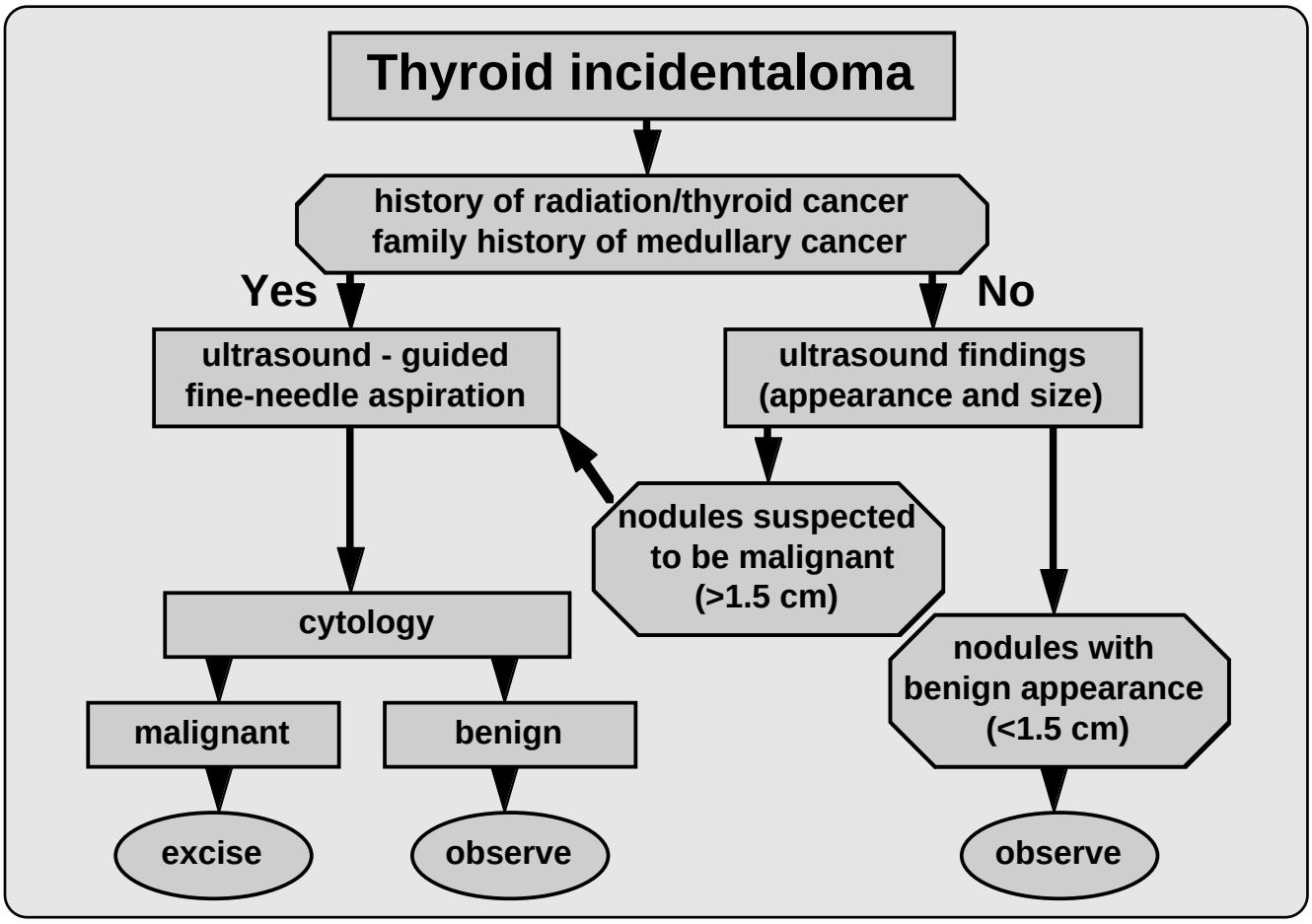
High resolution ultrasonography is pretty good at picking up thyroid nodules. Unfortunately no-one knows the significance of the nodules when found. What is certain is that only a small proportion of the glands will become malignant. Thus the imaging advance has created a new clinical problem, yet another example of what we have pointed out so often in ***Bandolier*** - that developments in diagnostic testing lead to and create increased demand for treatment services which have never been evaluated.

Tan & Gharib do more than leave us hanging there, though. They provide an algorithm outlining an approach to thyroid incidentalomas, which is a useful guide to what to do depending on history of radiation exposure, family history and ultrasound appearance.

Bandolier confidently predicts that the incidence of incidentalomas will increase.

Reference:

1 GH Tan, H Gharib. Thyroid incidentalomas: management approaches to nonpalpable nodules discovered incidentally on thyroid imaging. Annals of Internal Medicine 1997 126: 226-31.



QUALITY IMPROVEMENT BY AUDIT

Bandolier actively seeks examples of how delivery of healthcare can be done effectively - often called "doing the right thing right". Unfortunately such examples are rare. Given the academic slant of many of our medical journals, these must seem pretty mundane, and it must be hard to catch an editor's eye. So many thanks to a pharmacist friend of ***Bandolier*** for bringing to our attention a super example.

Pain relief after day surgery

In an eight week period in 1993, 150 adults having surgery in a day surgery unit in Cardiff (general surgery, gynaecology, ophthalmic or ENT) were audited using a postal questionnaire for pain at home after their operation. At 24 and 72 hours they rated their pain as mild, moderate or severe, and recorded analgesic drugs used over three days. The hospital had an analgesic prescribing policy which covered about half these patients.

The results of the audit showed that of the 111 usable questionnaires returned, 29 patients (26%) reported severe pain at at least one time, and 12 patients (11%) contacted their GP or were readmitted to hospital because of poor pain control. For some operations (hernia repair, for instance), almost all the patients had severe pain and over a third sought GP advice or were re-admitted.

Action taken

Briefly, the prescribing policy was revised to include 'missing' procedures. Procedures were ordered into those where mild pain was expected (cataracts, for example), moderate pain was expected (varicose veins, for example), or severe pain was expected (hernia repair, for example). Prescribing policy was adjusted to take account of the expected pain level:

Mild pain:	Paracetamol 1000 mg four times a day
Moderate pain:	Co-codamol 1 or 2 tablets four times a day
Severe pain:	Co-codamol 1 or 2 tablets four times a day plus naproxen 500 mg twice a day

(with, of course, appropriate adjustments for certain patients with ulcers or asthma).

In addition a system of 'rubber-stamping' prescription forms was devised so that appropriate prescriptions were given for appropriate operation types.

Results of this action

An audit of 200 patients over a 10 week period in 1994 showed that the prescribing policy was followed in 89% of cases. There were 130 returned questionnaires. They showed that the number of patients reporting severe pain at 24 or 72 hours at home had been reduced almost to zero (about 10% reporting severe pain in but four of 12 operation types). No patient had cause to contact their GP for provision of postoperative pain relief.

Comment

Simple really, when put like this. Some thought, some organisation, and a will to do things better, and everyone benefits.

Reference:

1 TK Haynes, DE Evans, D Roberts. Pain relief after day surgery: quality improvement by audit. The Journal of One-Day Surgery, Summer 1995, 12-15.

WHERE THERE IS HOPE, THERE IS LIFE?

Does hope help?

Bandolier is sometimes seen as dreadfully stuck in its ways of quantification and arithmetic, but we do recognise good studies and research projects in which the only numbers are page numbers. A paper on the meta-analysis of hope seems to us to be an example of high quality research in a very difficult field [1].

The paper is a review of 46 articles published between 1975 and 1993 on the effects of hope on outcome. The literature review lists many fascinating titles, for example:

> "The process of maintaining hope in adults undergo ing bone marrow transplantation for leukaemia";
>
> "Development of an instrument to measure hope";
>
> "Fostering hope in terminally ill people".

Hope and false hope

The giving or sustaining of hope, or its destruction, are the types of subtle intervention which take place in almost every clinical interaction but which are very rarely discussed or studied. A whole variety of different types of interventions may have been wrongly packaged together under the label of the "placebo" or "non-specific" effects of clinical practice, and the clinician's attitude towards hope is one of these.

Ontology and epistemology

Ontology is the study of being or existing, a metaphysical study. Epistemology is a bit more hard-nosed, being concerned with the study of how we know things, and of course, much of philosophy from Plato to A. J. Ayer is concerned with how we know. Research is itself part of the process of epistemology.

What the authors have done is to look at the papers, try to identify what sort of concepts are implicit in the simple four letter word "hope". It would be very nice to have found 15 good quality randomised trials in which some patients had been given hope and others had not, although the complexities of designing such a single blind trial make it extremely daunting.

The authors concentrated on "describing the essence of hope" as it was used in these 46 papers, most of which were descriptive studies. Their conclusion, not surprisingly, was that the term was too vague and diffuse for meta-analysis of any of the results of the studies to be possible, but it is a very good example of an attempt to tackle a complex, diffuse and difficult topic.

Without a clear definition of the intervention, evaluation of its effect by quantifiable means is impossible.

Effectiveness of giving patients hope

Unfortunately the paper comes to no conclusions, and does no analysis of any of the outcomes, not even a simple vote counting of whether the studies showed a link between outcome and hope. But the authors have identified the studies, and this would be a good place to start for anyone interested in studies on the effects of hope on patient outcome.

Reference

1 J Kylmä, K Vehviläinen-Julkunen, K. Hope in nursing research: a meta-analysis of the ontololgical and epistemological foundations of research on hope. Journal of Advanced Nursing 1997 25: 364-71

OLD CURIOSITY SHOP

The gonococcus and the toilet seat

The question being asked here is pretty obvious. Some researchers from Oregon tried to answer the question and published their results in the New England Journal in 1979 [1]. To test the hypothesis that toilet seats could serve as a reservoir for infectious agents they did two experiments. First they determined the survival of gonococci added in large quantities to toilet seats. Then they surveyed a number of 'restrooms' and cultured material from the toilet seats in them.

Results

Adding gonococcus (*N. gonorrhoeae*) to toilet seats and culturing the material added at various times up to four hours later showed the following.

1. Gonococci in a saline suspension could not be cultured from the toilet seat 10 minutes later.
2. Gonococci in a broth suspension could not be cultured from the toilet seat 10 minutes later.
3. Gonococci in a suspension containing saline and urethral discharge from patients with gonorrhoea could be cultured from toilet seats up to two hours later.

The survey of 72 mens' and womens' restrooms proved negative for the culture of *N. gonorrhoeae*. However, a number of other pathogens could be cultured, mostly skin pathogens. The top surfaces of the toilet seats were more heavily contaminated than the bottom surfaces.

Conclusion

While the bacteria which cause gonorrhoea could survive for several hours in dried purulent discharge on a toilet seat, the survey failed to find any. Nonsexual transmission from toilet seats is not impossible, just very unlikely. The authors give some interesting ways in which pathogens can be transmitted.

Reference:

1 JH Gilbaugh, PC Fuchs. The gonococcus and the toilet seat. New England Journal of Medicine 1979 301: 91-3.

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